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10/580,782	04/05/2007	Yoshiko Miura	TESHP104US	7126

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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
05/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/580,782	MIURA ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *May 26, 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/06, 11/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6-11 are pending in this application.

Sequence listing filed on May 10, 2010 has been accepted and entered.

Objection

1. The specification is objected to for the following reason: The peptide sequences disclosed throughout the specification and figure are missing the sequence identifiers (please see Figure 1 and paragraphs [0004], [0012], [0013], [0025], [0026], [0037], [0041], [0042], [0068]-[0076], [0080]-[0081], [0085], [0098], [0102] of US 2008/0023859, for example). The proper way to claim a peptide sequence is for example, VPGVGVPGVG (SEQ ID NO:1) (see 37 CFR 1.821(d)). These errors should be corrected.

Rejection

35 U.S.C. 112, second paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 6 recites parenthetical expression "(where x is any amino acid residue, L_1 and L_2 are linkers, SUGs are sugar chains, m is 0 or 1 and n is an integer from 1 to 10, and L_1 and L_2 may be identical with or different from each other and SUGs may be

identical with or different from each other)". The metes and bounds of claim 1 is rendered vague and indefinite by the parenthetical recitation of "(where x is any amino acid residue, L_1 and L_2 are linkers, SUGs are sugar chains, m is 0 or 1 and n is an integer from 1 to 10, and L_1 and L_2 may be identical with or different from each other and SUGs may be identical with or different from each other)" because it is unclear as to whether the limitation is part of the instantly claimed subject matter.

35. U.S.C. 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

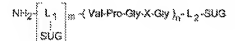
6. Claims 6-7 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the peptide VPGVG, does not reasonably provide enablement for all amino acids at position 4 of VPGVG The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount

of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (5) the breadth of the claims:

The claims are drawn to a temperature-responsive micelle comprising synthesized glycopeptides, the glycopeptides having the formula  , wherein x is any amino acid residue, L_1 and L_2 are linkers, SUGs are sugar chains, m is 0 or 1 and n is an integer from 1 to 10, and L_1 and L_2 may be identical with or different from each other and SUGs may be identical with or different from each other.

(2) The state of the prior art and (4) the predictability or unpredictability of the art::

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (Peptide Hormones, JA Parsons, Ed., 1976, 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by

painstaking experimental study" (see p. 6). Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Additionally, Schinzel et al (FEBS, 1991, 286(1, 2): 125-128) teach that the substitution of Lys^{539} by an arginine caused a 600 fold reduction, substitution of Arg^{534} by a glutamine caused an even larger 7000-fold reduction of the catalytic rate while substrate binding remained essentially unaffected. The reference teaches that Arg^{534} to Gln exchange reduces the catalytic rate near to inactivity and even the conservative Lys^{534} to Arg exchange caused marked decrease of activity (see abstract).

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the

lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Additionally, the art recognizes that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study". Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some

substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Therefore, any modification on the polypeptide might have an affect on the polypeptide, thus vast numbers of experimentation would be required to see if the polypeptide modified with the oxime-containing non-natural amino acid would have the same affect on certain diseases as the wild-type polypeptide. As with all peptides, activity is based on the structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. The sate of the art for prediction of the native conformation of the protein is, at best, a vague science. For example, in peptide chemistry, Ngo et al teach that for protein and peptides, a "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task" (see p. 493). Accordingly, it is not known if an efficient algorithm for predicting the structure exists for a protein or peptide from its amino acid alone (see p. 492). Thus, activity of a given peptide cannot be based on its structure alone. Similarly, the Rudinger article (see the conclusion in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from the case to case by painstaking experimental study." Finally, in an article published in Science, the author concluded that "one of the 'grand challenges' of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to

obtain" (see p. 643 in Berendsen). Berendsen et al states "at the present level of sophistication, [homology modeling] are effective for only 25% of the proteins for which the amino acid sequence is known" (see p. 642). It is known that proteins fold into their native conformation spontaneously and within seconds. The underlying principle of folding is known in the art yet the art lacks the ability to mimic native folding process (see p. 642 in Berendsen). "[E]xisting computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure;...we are not too sure that the available force field descriptions, which we need to compute the energy of a each configuration, are accurate enough to come up with reliable free energy of a conformation" (see p. 642 in Berendsen). Berendsen et al discloses the principle of the "Levinthal's paradox" which states that if one was to assume that "three possible states for every flexible dihedral angle in the backbone of a 100 protein residue, the number of possible backbone configuration is 3^{200}. Even an incredibly fast computational or physical sample in 10^{-15}s would mean that complete sample would take 10^{80}s, which excides that age of the universe by more than 60 orders of magnitude." Other tools such as lattice models provide insight into principle of folding, but to provide no solutions to the real folding problems (see p. 643 in Berendsen). The art has recognized that even single point mutations can cause diverse effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle

cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type VPGVG glycopeptide.

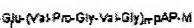
Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any glycopeptide that has the same activity as the claimed peptide, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification discloses the CD spectrum of VPGVGVPGVG (see Figures 8 and 9). The specification discloses compounds 1 ( ), 4

(

), and 8 (

) (see Figure 1). These all have the glycopeptides sequence VPGVG. The specification discloses that the preferred peptide has the Val for X in the sequence (see paragraph [0038]). The specification discloses that "there is no limitation regarding a linker between a peptide and a sugar chain so long as the linker has organic groups bonding the peptide and the sugar chain…L_2 at the C-terminal side is preferably paraamidephenoxide, alkylamine, ethyleneglycol amine or the like" (see paragraphs [0034]-[-0035]). The working example describes the peptides Fmoc-VPGVGVPGVG, Fmoc-VPGVG, Fmoc-EVPGVG, Ac-VPGVGVPGVG, Ac-EVPGVGVPGVG (see paragraphs [0068]-[0073]). Compounds 1, 4 and 8 all have the sequence VPGVGVPGVG. The specification does not describe any other peptide that have temperature sensitivity, such as any other type of peptide or peptide-like molecule that function to have temperature sensitivity. Description of a pentapeptide repeats (VPGVG) is not sufficient to encompass numerous other peptides and oligopeptides that belong to the same genus. For example, there are varying amino acid compositions, and numerous distinct qualities that make up the genus. There are 20 naturally occurring amino acids and vast numbers of non-natural amino acids, protected amino acids, modified amino acids, amino acid mimetics and so forth. There are numerous different pentapeptide possibilities. The specification however, does not provide for the myriad of oligopeptides embraced by the broad genus claimed. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. Since

there are 20 naturally occurring amino acids, and vast amount of other non-naturally occurring amino acids, the possibilities are vast.

(8) The quantity of experimentation necessary:

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any glycopeptides having the sequence VPGXG, X being any amino acid and any compounds as linkers superposed in between sugars and glycopeptide that has the same activity as the claimed protein, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

7. Claims 6-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude

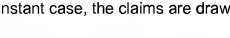
that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a temperature-responsive micelle comprising synthesized glycopeptides, the glycopeptides having the formula  , wherein x is any amino acid residue, L_1 and L_2 are linkers, SUGs are sugar chains, m is 0 or 1 and n is an integer from 1 to 10, and L_1 and L_2 may be identical with or different from each other and SUGs may be identical with or different from each other. The generic statement L_1 and L_2 are linkers… and L_1 and L_2 may be identical with or different from each other does not provide ample written description for the compounds since the claims do not describe a single structural

feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 6 is broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of compounds that functions as a linker to link two compounds together. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void of organic molecules, peptidomimetics, synthetic compounds and organic compounds that functions as a peptide-like molecule that qualify for the functional characteristics claimed as a linker.

The specification discloses that "there is no limitation regarding a linker between a peptide and a sugar chain so long as the linker has organic groups bonding the peptide and the sugar chain…Linker L_2 is preferably paramidephenoxide, alkylamine,

ethyleneglycol amine or the like...L_1 is a linker for bonding a sugar chain to the N-terminal side of the peptide chain, preferably by incorporating an amino acid having a carboxyl group such as glutamic acid or an aspartic acid into the peptide chain, the linker easily bond sugar chains through the additional linker that is similar to the linker L_2" (see paragraphs [0034]-[0036]). The working example describes the linker paraamidephenoxide and glutamic acid (see paragraphs [0042]-[0049] and [0080]). The specification does not describe any other linkers, such as synthetic polymers comprising repeating polypeptide units, or any other organic compounds. Description of paraamidephenoxide and glutamic acid is not sufficient to encompass numerous other organic compounds that functions as linkers that belong to the same genus. For example, there are varying lengths, varying amino acid compositions, varying organic compositions and numerous distinct qualities that make up the genus. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

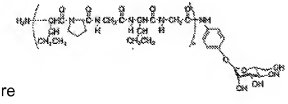
35 U.S.C. 102

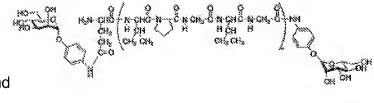
8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

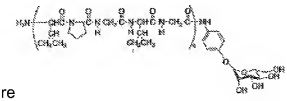
9. Claims 6-9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Miura et al (Polymer Preprints, Japan, 9/24/2003, 52(13): 3771-3772, translation, filed with IDS).

10. Miura et al teach compounds having the

structure 

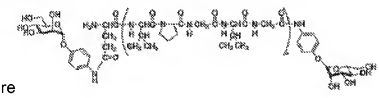
and  , wherein n is 1 or 2 (see Figure 1, p. 3771, and page 1 of translated page), meeting the limitation of instant claims 6-9 and 11. The peptide sequence is a pentamer VPGVG, meeting the limitation of instant claims 6 and 8. The compounds have monosaccharides mannose, meeting the

limitation of claim 7. The elastin compound having the



structure , meets the limitation of claims 6 and 9.

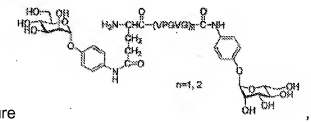
The elastin compound having the



structure , meets the limitation of instant claims 6-8. Since the reference teaches all of the active components of instant claims 6-9 and 11, this would inherently have all of the characteristics and properties of instant claim 11. The MPEP § 2112 states: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the Examiner presents evidence or reasoning tending to show inherency, the burden shifts to the Applicant to show an unobvious difference '[t]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on *prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977))."

Thus, the reference anticipates instant claims 6-9 and 11.

11. Claims 6-8 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Shibata et al (Polymer Preprints, Japan, 5/28/2003, 52(5): 1066, translation, filed with IDS).

12. Shibata et al teach glycopeptide having α-mannose at the terminals of elastin model peptide (see translated page 1, first paragraph). The reference teaches the glycopeptides having the structure  , meeting the limitation of instant claims 6-8 and 11. Since the reference teaches all of the active components of instant claims 6-8 and 11, this would inherently have all of the characteristics and properties of instant claim 11. The MPEP § 2112 states: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the Examiner presents evidence or reasoning tending to show inherency, the burden shifts to the Applicant to show an unobvious difference '[t]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on *prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In*

re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977))."

35 U.S.C. 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

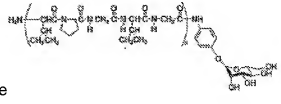
14. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

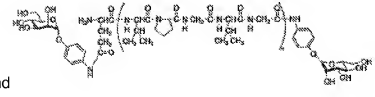
15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

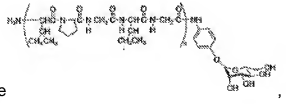
16. Claims 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miura et al (Polymer Preprints, Japan, 9/24/2003, 52(13): 3771-3772, translation, filed with IDS) in view of Smith et al (US Patent No. 4,966,848) or Peers et al (US Patent No. 5,837,218) or Smith et al (US Patent No. 5,223,421).



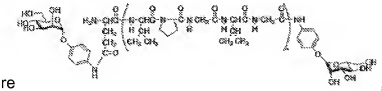
Miura et al teach compounds having the structure



and , wherein n is 1 or 2 (see Figure 1, p. 3771, and page 1 of translated page), meeting the limitation of instant claims 6-9 and 11. The peptide sequence is a pentamer VPGVG, meeting the limitation of instant claims 6 and 8. The compounds have monosaccharides mannose, meeting the limitation of claim 7. The elastin compound having the



structure , meets the limitation of claims 6 and 9. The elastin compound having the

structure  , meets the limitation of instant claims 6-8. Since the reference teaches all of the active components of instant claims 6-9 and 11, this would inherently have all of the characteristics and properties of instant claim 11. The MPEP § 2112 states: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the Examiner presents evidence or reasoning tending to show inherency, the burden shifts to the Applicant to show an unobvious difference '[t]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on *prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977))."

The difference between the reference and the instant claims is that the reference does not teach a protecting group present at the N-terminal of the glycopeptides.

17. However, Smith et al (US Patent '848) teach that "An acetyl moiety was discovered as the amino-terminal blocking group of viral coat protein in 1958 and of hormonal peptide in 1959. Since then, a large number of proteins in various organisms have been shown to possess acetylated amino-terminal residues. For example, mouse

L-cells and Ehrich ascites cells have about 80% of their intracellular soluble proteins Nα-acetylated [and in] lower eukaryotic organisms, about 50%. These data demonstrate that N—acetyl is a very important blocking group. It has been suggested that the biological function of this blocking group may be to protect against premature protein catabolism and protein proteolytic degradation." (see column 1, lines 18-37).

18. Peers et al (US Patent '218) teach that, "N- and C-terminal modification of peptides is common practice in the art of preparation of peptides having greater stability, particularly for *in vivo* use. Such modifications include the action of protecting groups such as the protecting groups used conventionally in the art of organic synthesis. Suitable N-terminal protecting groups include, for example, lower alkanoyl groups of the formula R-C(O)- in which R is a linear or branched lower alkyl…A preferred group for protecting the N-terminal end of the present compounds is the acetyl group, $CH_3C(O)$" (see column 3, lines 15-25). The reference further teaches that "suitable C-terminal protecting groups include groups which form ketones or amides at the carbon atom of the C-terminal carboxyl, or groups which form esters at the oxygen atom of the carboxyl. Ketone and ester-forming groups include alkyl groups, particularly branched or unbranched lower alkyl" (see column 3, lines 28-33).

19. Smith et al (US Patent '421) teach that, "Nα-acetylation is the most common chemical modification of the α-amino acid group at the amino termini of eukaryotic proteins" (see column 3, lines 62-64). Additionally, "the rate of protein turnover mediated by the ubiquitin-dependent degradation system depends on the presence of a free α-amino group at the amino terminus of model proteins and [indicates that] Nα-acetylation

may play a crucial role in impeding protein turnover. Thus, Nα-acetylation plays important roles in regulating diverse protein functions" (see column 4, lines 21-40).

20. Therefore, it would have been obvious to one of ordinary skill in the art to have N-acetylated modified peptides for the benefit of protecting the peptide from proteolytic degradation and premature protein catabolism. One would have been motivated to acetylate the N-terminus, in order to mimic 'the most common chemical modification' of eukaryotic proteins, protect the peptide from proteolytic degradation and premature catabolism, as protecting the N- and C-terminus is 'common practice in the art' (see Peers, supra) and acetyl group is 'a very important blocking group' (Smith, supra). One would have had a reasonable expectation of success in forming these N- and C-terminal modified peptides, because it is 'common practice in the art' (Peers, supra) to modify the N-terminus with the most common chemical modification' of eukaryotic proteins (Smith, supra), and is a technique practiced widely in the art (Peers and Smith, supra).

21. Claims 6-8, 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibata et al (Polymer Preprints, Japan, 5/28/2003, 52(5): 1066, translation, filed with IDS) in view of Smith et al (US Patent No. 4,966,848) or Peers et al (US Patent No. 5,837,218) or Smith et al (US Patent No. 5,223,421).

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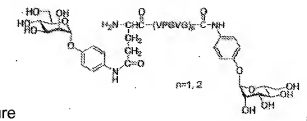

glycopeptides having the structure , meeting the limitation of instant claims 6-8 and 11. Since the reference teaches all of the active components of instant claims 6-8 and 11, this would inherently have all of the characteristics and properties of instant claim 11. The MPEP § 2112 states: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the Examiner presents evidence or reasoning tending to show inherency, the burden shifts to the Applicant to show an unobvious difference '[t]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on *prima facie* obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977))."

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Conclusion

26. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654